

THAT WHICH IS CLAIMED:

1. A method for treating a human subject for chronic lymphocytic leukemia (CLL), comprising administering to said subject an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said monoclonal antibody being free of significant agonist activity, whereby, when said monoclonal antibody binds to the CD40 antigen expressed on the surface of said cell, the growth or differentiation of said cell is inhibited, said human anti-CD40 monoclonal antibody being selected from the group consisting of:
- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
 - b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
 - d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
 - e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
 - f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
 - g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
 - h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

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- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly
5 produced; and
- k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.
- 10 2. The method of claim 1, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.
3. The method of claim 1, wherein said fragment is selected from the
15 group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.
4. A method for treating a human subject for chronic lymphocytic leukemia (CLL), comprising administering to said subject an effective amount of an
20 antagonist anti-CD40 monoclonal antibody that specifically binds Domain 2 of human CD40 antigen, wherein said antibody is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.
5. The method of claim 4, wherein said antibody is a human antibody.
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6. The method of claim 4, wherein said antibody is recombinantly produced.
7. The method of claim 4, wherein said antibody has the binding
30 specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.

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8. The method of claim 4, wherein said antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.

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9. The method of claim 4, wherein said antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

10. The method of claim 4, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

11. The method of claim 4, wherein said antibody is selected from the group consisting of:

- 15 a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
- 20 b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- 25 c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;
- d) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay;
- 30 f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and

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g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-f), where the fragment retains the capability of specifically binding to said human CD40 antigen.

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12. A method for inhibiting the growth of chronic lymphocytic leukemia (CLL) cells expressing CD40 antigen, said method comprising contacting said cells with an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to said CD40 antigen, said monoclonal antibody being free of significant agonist activity when bound to CD40 antigen, wherein said antibody is selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- 15 c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
- 20 d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
- 25 e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- f) a monoclonal antibody that binds to an epitope capable of binding the
30 monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

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- h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- 5 j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and
- k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment
- 10 retains the capability of specifically binding to said human CD40 antigen.

13. The method of claim 12, wherein said monoclonal antibody binds to human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

15 14. The method of claim 12, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

20 15. A method for inhibiting the growth of chronic lymphocytic leukemia (CLL) cells expressing CD40 antigen, said method comprising contacting said cells with an effective amount of an antagonist anti-CD40 monoclonal antibody that specifically binds Domain 2 of human CD40 antigen, wherein said antibody is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.

25 16. The method of claim 15, wherein said antibody is a human antibody.

17. The method of claim 15, wherein said antibody is recombinantly produced.

30 18. The method of claim 15, wherein said antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.

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19. The method of claim 15, wherein said antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the
5 hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.

20. The method of claim 15, wherein said antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

10 21. The method of claim 15, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

22. The method of claim 15, wherein said antibody is selected from the
15 group consisting of:

a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID
20 NO:2 and SEQ ID NO:5;

b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

25 c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

d) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

e) a monoclonal antibody that competes with the monoclonal antibody
30 CHIR-12.12 in a competitive binding assay;

f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and

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g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-f), where the fragment retains the capability of specifically binding to said human CD40 antigen.

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